TOPIC 32 – Congenital heart defects

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Defects of cardiac conduction system in Tbx1 null mutant

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The ventricular conduction system (VCS) is responsible for the rapid propagation of electrical activity in the ventricles. The VCS is composed of the His bundle, the right (RBB) and left (LBB) bundle branches and the peripheral Purkinje fibers (PF). TBX1 is a major candidate gene for DiGeorge syndrome, characterized by craniofacial defects and cardiac malformations including tetralogy of Fallot. Multiple defects found in the human syndrome can be observed in Tbx1 null mouse embryos. Among these, Tbx1 mutant embryos display a common arterial trunk and a ventricular septal defect (VS D). In order to analyze the development of the VCS in Tbx1 null hearts, we have crossed Tbx1±with the Cx40-GFP mice to easily identify conductive myocytes. At E18.5, Tbx1 null hearts present a non-compact His bundle and a disconnection of the RBB with the PF network abnormally localized at the base of the right septal papillary muscle up to the VS D. Moreover, the right septal papillary muscle is enlarged and malformed. Using 3D reconstruction of isolated septa, we have clearly demonstrated the absence of the proximal RBB in Tbx1 mutant hearts, and the presence of a hypoplastic His bundle positioned more anteriorly in comparison to control hearts. Electrical activation maps of Tbx1 mutant hearts reveal an exclusively left ventricular activation while two breakthroughs in the right and left ventricles are observed in control hearts. This study revealed that the Tbx1 mutants display a RBB block. We carried out a detailed morphological and functional characterization of the His bundle and RBB at earlier stages. At E14.5, the His bundle is positioned more anteriorly in Tbx1-/- hearts compared to controls. No significant differences were observed by optical mapping in Tbx1 mutant hearts. To conclude, our data strongly suggest that a defect in cardiac morphogenesis may be at the origin of conduction defect.

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Ebstein's disease in adulthood

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Background: Ebstein's disease is a rare congenital heart malformation, occurs in approximately 1 to 5 per 200,000 live births, with various clinical presentations depending on the age at diagnosis and the severity of the anatomical pattern.

Objective: The aim of this study is to determinate the clinical presentation, the echocardiographic patterns and the outcome of this malformation in adulthood.

Methods and Results: Retrospective study about 10 cases of Ebstein's anomaly in adult patients (5 women and 5 men); the mean age was 32±13.9 years old [16; 61]. The clinical manifestations were absent in 3 patients, arrhythmic manifestations (palpitations, lipothymia, syncope) were noted in 5 patients and congestive heart failure was observed in 2 patients. Electrocardiogram revealed Wolf-Parkinson-White syndrome in 3 cases, conduction abnormalities in 5 cases and ventricular excitability in 2 cases. Transthoracic echocardiography confirmed the diagnosis of Ebstein anomaly in all cases, showing apical displacement of the septal leaflet of the tricuspid valve. Three patients had the A grade of the Carpentier's classification and the others had the grade B. Only one patient underwent a surgical repair because a refractory heart failure. Anti arrhythmic and hemodynamic therapy was administrated in 6 and 4 patients respectively. After an outcome of 6.5 years, arrhythmic and hemodynamic complications occurred in 3 patients and no death.

Conclusion: Clinical presentation and outcome of Ebstein's anomaly varies considerably by anatomic severity and many cases are discovered in adults. The prognosis is worsening by arrhythmia and heart failure. Optimal timing of intervention is often difficult and must be individualized. Conservative surgery and anti arrhythmic therapy had enhanced the prognosis of this congenital heart malformation.

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Diagnosis and management of Anomalous origin of the Left Coronary Artery from the Pulmonary Artery (ALCAPA syndrome) in a series of 9 adult patients

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ALCAPA syndrome is a rare congenital heart disease that is mainly diagnosed during the first months of life with a high early mortality in symptomatic children in the absence of surgery. Adult form is extremely rare and no recommendation for the management of this form is available. We undertook this study in order to analyze initial symptoms and the management of adult pts with ALCAPA.

Methods: We analyzed retrospectively the data of 9 adults (49±16 years, 3M) from the charts of Cardiology Departments of 5 French hospitals (Argenteuil, Bordeaux, Brest, Lille, Nantes and Rennes).

Results: Symptoms consisted of chest pain (44.4%), *supra*-ventricular arrhythmia (33%) and heart failure (25%). ECG showed negative T waves or ST segment depression in antero-septal leads in 43% of pts. Echocardiogram showed a mean LVEF of 46±12.6% with kinetic abnormalities in 57% of the pts. Mitral regurgitation was present in all pts but was mainly moderate (71%). Coronary angiography was performed in 85.7% of pts and showed ALCAPA in all cases. CT-scan, MRI and myocardial scintigraphy were performed for diagnosis respectively in 57, 43 and 55.5% of the cases but more often for follow-up (FU). Reconstructive surgery was performed in 8 pts and a mitral valve reconstruction in one pt. Another pt underwent 4 CABG several years later. Immediate post-operative complications were: cardiogenic shock (2 pts), non-significant narrowing of the transferred coronary artery ostium that was treated medically (1 pt). One 70 year-old pt refused surgery. He died 2 years later. Medical treatment was used in 77.8% of pts: ACEI (22.2%), beta-blockers (44.4%) or anti-platelet agent (11.1%). A prophylactic ICD was implanted in one pt. All operated pts are alive with a FU of 26±24 years.

Conclusion: Diagnosis of ALCAPA in adult pts is very rare and is done mainly by coronary angiography in the presence of chest pain or heart failure. The results of surgery in addition to medical treatment are excellent.

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Anatomy of the ventricular septal defect in congenital heart defects: a random association?

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Introduction: A ventricular septal defect (VS D) is part of most congenital heart defects (CHD).

Objective: To determine the distribution of the anatomic types of VS D in CHD.

Methods: We analysed 1178 heart specimens with CHD, focusing on the localization of the VS D: muscular, membranous, outlet between the two limbs of

the septal band, inlet. The specimens were classified according to the anatomic and clinical classification of CHD (ACC-CHD).

Results: 67% of hearts had a VS D:

- constant, of a single type, in tetralogy of Fallot and variants and common arterial trunk (outlet), in complete atrioventricular canal (CAVC, inlet), and in double inlet left ventricle (DILV, muscular).
- not constant with a predominant type, in 96% of double discordance (DD,inlet 82%), 62% of heterotaxy syndromes (Hetx, inlet 93%), 93% of interrupted aortic arch (outlet 80%), 87% of double outlet right ventricle (outlet 77%).
- not constant, of variable type, in 68% of aortic coarctation (CoA: outlet 44%, membranous 35%, muscular 21%), 54% of transposition of the great arteries (TGA: outlet 40%, membranous 25%, muscular 25%, inlet 10%).
- rare, in anomalies of pulmonary veins (5%), Ebstein (14%), double inlet right ventricle (10%), coronary anomalies (25%).
- isolated in 10% of all VS D: outlet 44%, membranous 36%, muscular 18%, inlet 2%.
- Major associations according to VS D type:
- outlet: 60% "conotruncal" defects (CTD), 10% TGA
- inlet: 57% CAVC, 13% DD, 10% Hetx
- muscular: 33% DILV, 26% TGA, 13% isolated
- membranous: 30% TGA, 28% isolated, 16% CoA.

Conclusion: The VS D is an integral part of the phenotype in some CHD. In CoA and TGA the VS D is not constant and its anatomic distribution is similar to that in isolated VS D, indicating a likely random association. This reinforces the hypothesis of different genetic mechanisms in TGA and CTD. This original approach, using the anatomic characteristics of one part of the phenotype, could provide new insights in the grouping and aetiology of CHD.

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Influence of the location of the defect in Eisenmenger patients

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Background: Eisenmenger syndrome (ES) is the most advanced form of pulmonary arterial hypertension (PAH) related to congenital heart disease. Several studies have suggested that the location of the shunt causes differences in natural course and circulatory physiology between patients with ES. We therefore aimed to compare echocardiographic parameters and clinical variables in various types of ES.

Methods and Results: In this longitudinal cohort study, 186 patients with ES and non-complex congenital heart disease were recruited, 34 with pre-tricuspid and 152 with post-tricuspid shunt (75 ventricular septal defect (VS D), 57 complete atrio-ventricular septal defect (AVS D), 16 patent ductusarteriosus (PDA), 3 truncusarteriosus, 1aorto-pulmonary window). Patients with post-tricuspid shunts were younger in our cohort ($p<0.001$), they had higher BNP concentrations and reduced exercise tolerance compared to patients with post-tricuspid shunts. Right ventricular (RV) function was impaired in patients with ASD with larger right ventricles, impaired systolic function and adaptation. Pre-tricuspid defects patients also exhibit larger atria and raised right atrial pressure. Overall, the left ventricular eccentricity index was significantly raised in ASD patients compared to others. Within post-tricuspid shunts, patients with AVS D had improved right ventricular function, whereas patients with PDA had decreased RV function.

Conclusion: Cardiac physiology and chronic adaptation in ES differ widely according to the location of the defect. Differences in RV function and adaptation are important between patients with pre- or post-tricuspid shunts and should be incorporated in the interpretation of echocardiography in ES.The improved RV function likely accounts for the prolonged course of PAH in patients with post-tricuspid shunt in the setting of ES compared to patients with ASD or other types of PAH.

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The influence of closure of patent ductus arteriosus on left and right ventricular sizes and functions

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Background: Patent ductus arteriosus is responsible for left ventricular diastolic and rignt ventricular systolic overload. Little is known about hemodynamic changes after percutaneous and surgical closure.

Methods: We conducted a bicentric prospective study of children with patent ductus arteriosus, evaluating the evolution of systolic and diastolic ventricular functions before, 1 day and 1 month after successful closure, by means of transthoracic echocardiography.

Results: 33 children, age 3 months to 14.5 years, received successful closure of their patent ductus arteriosus, 32 percutaneously and 1 surgically. All patent ductus arteriosus were closed for hemodynamic reasons, with a mean diameter of 3.6±0.9 mm. There was a significant increase in systolic (100.6±15.1 versus 95.4±15.3 mmHg, $p<0.05$) and diastolic (53.2±17.1 versus 47.8±17.2 mmHg, $p<0.05$) blood pressures, immediately after the suppression of the shunt. Left ventricular fractional shortening and end diastolic volumes index were significantly tlower the day after closure (respectively 34.7±5.5 versus 37.8±4.7% and 47±16.2 versus 54.6±20.1 mL/m^2) and remained low compared to the preclosure state at follow-up (respectively 33.8±5.4 versus 37.8±4.7% and 47±12.7 versus 54.6±20.1 mL/m^2). A non significant decrease in left ventricular filling pressures was observed. Right ventricular systolic parameters (TAPSE) were significantly lower 1 month after closure (19.3±2.9 versus 21.4±4.4 mm, $p<0.05$).

Conclusion: Changes in left ventricular volumes and function and in right ventricular function occur immediately after patent ductus arteriosus closure, and remain at 1 month of follow-up. Further studies are warranted to increase the number of patients and the duration of follow-up.

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Fetal tachycardia: outcomes over twenty years in five institutions in northern France

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Background: Fetal tachycardia is a rare disease that may result in serious morbidity and intra-uterine mortality.

Aims: The purpose of our study was to review the natural history of patients with fetal tachycardia, to determine the incidence of post-natal arrhythmia and to understand the gravity of hydrops in this population.

Methods and Results: We reviewed 34 gravidas admitted for fetal tachycardia between 1992 and 2012, in 5 centers in northern France Twenty-four had atrial flutter and ten had *supra*-ventricular tachycardia. Fetuses with hydrops were complicated of premature age delivery ($p=0.025$), lower birth weight ($p=0.022$) and required oral intubation ($p=0.025$). Amiodarone was used in forteen fetuses and was complicated with transient hypothyroidism ($p=0.006$). We report no neurological issues in our population. 47% presented post-natal arrhythmia. Patients with *supra*-ventricular tachycardia were still treated after one year ($p=0.011$). Post natal outcome is good with a majority of patients weaned off medication after one year even if we report three fetal deaths. Among the resistive tachycardias, we found three permanent junctional reciprocating tachycardias (including one requiring radiofrequency ablation at adult age) and one junctional ectopic tachycardia.

Conclusion: Mortality rate is low in patients with fetal tachycardia, even though the incidence of post-natal arrhythmia is high. The need of cesarean should be discussed for well-tolerated tachycardias. Patients with hydrops are associated with a poor prognosis and still represent a challenge to treat.